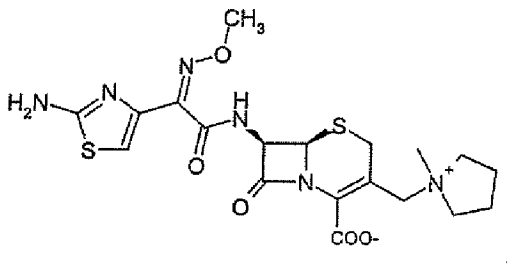
AUSTRIAN APPLICATION NO. 586/2003
(the '586 application)

Organic compounds

The present invention relates to the preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxy-imino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate (cefepime dihydrochloride monohydrate). Cefepime is a valuable 4th generation injectable cephalosporin with antibacterial properties, see e.g. The Merck Index Thirteenth Edition, Item 1935.

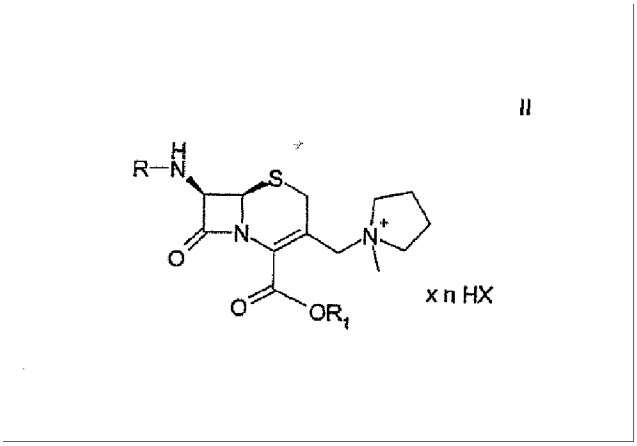



I

The preparation of cefepime is not simple. For example, it is known that the 7-acyl side chain as the difficult-to-obtain 2-(2-aminothiazol-4-yl)-2-methoxy-imino-acetic acid chloride hydrochloride must be used for the production of cefepime, in order to obtain an active ingredient which is pure in respect of the by-products anti-isomer and Δ-2 isomer.

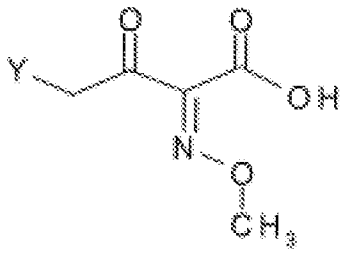
A novel process has now been found which solves the abovementioned problems.

The process comprises reaction of the β-lactam intermediate of formula II

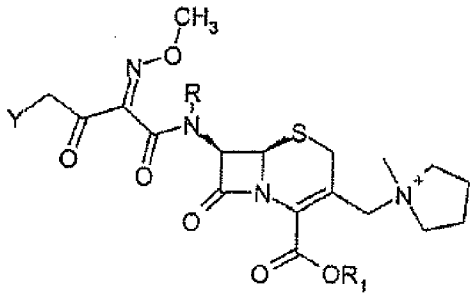



wherein

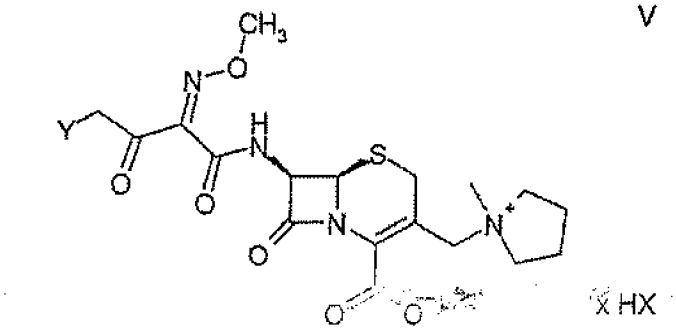
$R_1$ is a negative charge or trialkylsilyl,
R is H or trialkylsilyl,
n is 0 - 2 and
X is chloride, bromide or iodide,
with a reactive derivative of the compound of formula III




wherein Y is halogen,
to form a compound of formula IV



the silyl protecting groups - if present - are removed, if necessary the intermediate step of formula V



V

---

is isolated, the compound of formula IV, or the compound of formula V, is reacted with thiourea and subsequently the compound of formula I is isolated.

Y denotes chloride or bromide.

The compound of formula II may be used in free base form, as a mono-addition salt or as a di-addition salt with a hydrohalic acid such as hydrochloric acid, hydrobromic acid or hydriodic acid. The addition salts may additionally be present in solvated form.

If the silylation variant is chosen, the intermediate of formula II is obtained by methods known per se, using a silylation agent such as N,O-bis-(trimethylsilyl)-acetamide (BSA), N,O-bis-(trimethylsilyl)-trifluoroacetamide (BSTFA), N-methyl-N-trimethylsilyl-trifluoroacetamide (MSTFA) or for example hexamethyldisilazane (HMDS), in a solvent that is inert towards silylation agents, for example a nitrile, such as acetonitrile, an ether, for example tetrahydrofuran, or a chlorinated hydrocarbon, for example dichloromethane.

Subsequently, the silylated derivative of formula II is acylated with a reactive derivative of formula III, the reactive derivative being an acid chloride, acid bromide or active ester, for example a S-mercapto-benzothiazolyl ester, optionally in the presence of an auxiliary base such as a tertiary alkylamine.

The compound of formula IV is subsequently desilylated with the assistance of a protic reagent, for example water or an alcohol, and then the compound of formula IV is reacted with thiourea in an aqueous or organic-aqueous medium. The title compound is subsequently crystallised, if necessary after separating the organic solvent, and where appropriate after removing any salt that is present, for example after treatment using anion exchangers by methods known per se after adding hydrochloric acid from an aqueous acetonic solution.

An alternative is to work in an aqueous or aqueous-organic system, for example in a one-phase system consisting of water and a water-miscible solvent, for example a ketone, such as acetone, a nitrile, such as acetonitrile, or an ether, such as tetrahydrofuran, or in a two-phase system, for example in a combination of an ester of acetic acid, for example ethyl acetate, a chlorinated hydrocarbon, for example dichloromethane, or for example an aromatic, for example toluene, and the compound of formula II is optionally released from its mono- or di-addition salt with the assistance of a base, for example caustic soda solution or caustic potash solution, a sodium or potassium hydrogen carbonate or alkali carbonate, or by methods known per se using an ion exchanger, and subsequently the compound of formula II is acylated with a reactive derivative of formula III. After the acylation reaction has taken place, thiourea is added, and optionally after separating the organic solvent, the title

compound is isolated by methods known per se by adding acetone from an aqueous/acetonic solution.

If desired, it is possible to isolate the compound of formula IV, as an addition salt with a hydrohalic acid, for example as the hydrochloride. Here, the reaction sequence preferably starts with an acid addition salt of the compound of formula II, via the silylation route. By adding small amounts of protic solvent, for example water or an alcohol, to the compound of formula IV wherein $R_1$ and R preferably denote trialkylsilyl, the silyl groups are removed, and the halide present in the system enables direct crystallisation of the compound of formula V to take place. The preferred mono-addition salt is the monohydrochloride in crystalline form. In order to produce this, the compound of formula II is preferably used as the mono- or di-hydrochloride addition salt, and the preferred solvents for crystallisation are acetonitrile in combination with isopropanol.

The examples below elucidate the invention in more detail.

Example 1

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(4-chloro-2-methoxyimino-3-oxo-butyryl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium hydrochloride

1.55 g of N,O-bistrimethylsilylacetamide are added dropwise at room temperature to a suspension of 0.835 g of NMP-ACA.2HCl in 10.5 ml of acetonitrile. After stirring for 25 mins at room temperature, the solution obtained is cooled to -35°C. At this temperature, a solution of 4-chloro-2-methoxyimino-3-oxo-butyryl chloride in acetonitrile (for preparation see example

1a), which has been cooled to -20°C, is added. After stirring for 1 hour in a cooling bath at -35°C, 2 ml of isopropanol are added dropwise. The resulting suspension is heated to 0°C and stirred for 1 hour in an ice bath. The suspension is then filtered. The filter cake is washed with acetonitrile. After drying in a vacuum at room temperature, 1.42 g of product is obtained as a white crystalline powder.

$^1$H-NMR spectrum (DMSO-d6, δ in ppm)
1.957 - 1.690 (m, 2H, pyrrolidinyl-H); 2.943 (s, 3 H, N-CH3); 3.371 - 3.701 (m, 5 H, pyrrolidinyl-H, S-CH2); 3.866 (1 H, J = 10.0 Hz, S-CH2); 4.060 (s, 3 H, OCH3); 4.329 and 4.597(ABq, 2 H, J = 13.7 Hz, -CH2-N); 4.846 (s, 2 H, CH2C1); 5.322 (d, 1 H, 5.1 Hz, H6); 5.884 (dd, 1H, J = 8.4 Hz, J - 5.1 Hz, H7); 9.555 (d, IH, NH)

Example 1a

Preparation of 4-chloro-2-methoxyimino-3-oxo-butyryl chloride

A solution of 0.488 g of 4-chloro-2-methoxyiminobutyric acid in 8.0 ml of acetonitrile is mixed at -20°C with 0.353 g of chloromethylene iminium chloride (Vilsmeier reagent) and stirred for 1 hour at -20°C.

Example 2

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate (cefepime dihydrochloride monohydrate)

0.990 g of 1-[[(6R,7R)-7-[[(2Z)-(4-chloro-2-methoxy-imino-3-oxo-butyryl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium hydrocholoride are added at 4°C to a

solution of 0.152 g of thiourea in 5 ml of $H_2O$. The pH of the suspension is adjusted to pH 6.0 with ion exchanger LA-2 and maintained in the pH range of 5.5 to 6.0 by adding LA-2 dropwise. After stirring for 8.5 hours at 2 to 4°C, the reaction mixture is washed with 10 ml of methylene chloride. After phase separation, the aqueous phase is washed a second time with 10 ml of methylene chloride. The organic phases are combined and then extracted with 3 ml of $H_2O$. The aqueous phases are combined and mixed with 0.20 g of activated carbon. After stirring for 10 minutes, the carbon suspension is filtered. The carbon cake is washed with 1.5 ml of $H_2O$. The filtrate and washing water are combined, acidified with 6 m HCl to pH 0.6 and mixed with 50 ml of acetone. After adding seed crystals, stirring is effected for 15 minutes at room temperature, and then 50 ml of acetone is added dropwise over the course of 1 hour. The crystal suspension obtained is cooled to 0°C. After stirring for 1 hour in an ice bath, the suspension is filtered and the filter cake is washed with acetone. After drying in a vacuum at room temperature, 0.561 g of the title compound are obtained in the form of a white crystalline powder.

HPLC purity: 99.6 area %

Example 3

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate (cefepime dihydrochloride monohydrate)

1.55 g of N,O-bistrimethylsilylacetamide are added dropwise at 1°C to a suspension of 0.835 g of pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-dihydrochloride in

10.5 ml of acetonitrile. After stirring for 45 mins in an ice bath, the solution obtained is cooled to -35°C. At this temperature, a solution of 4-chloro-2-methoxy-imino-3-oxo-butyryl chloride (for preparation see example 1a), which has been cooled to -20°C, is added. After stirring for 1 hour in a cooling bath at -35°C, 2 ml of $H_2O$ are added dropwise. After stirring for 10 minutes at -35°C, 0.38 g of thiourea are added. The reaction mixture is subsequently heated to 0°C and the pH is adjusted to 6.0 by adding ion exchanger LA-2, and is maintained at this pH. After stirring for 2 hours in an ice bath, the 2-phase reaction mixture obtained is mixed with 2 ml of $H_2O$. After stirring for a further 16 hours at 0 to 4°C, the pH is acidified to pH 0.60 with 6 m HCl. After adding 50 ml of methylene chloride, the phases are separated. The methylene chloride phase is then extracted with 3 ml of $H_2O$. The aqueous phases are combined and mixed with 0.10 g of activated carbon. After stirring for 10 minutes, the activated carbon suspension is filtered. The carbon cake is washed with 1 ml of $H_2O$. The filtrate and washing water are combined and diluted with 30 ml of acetone. After adding seed crystals, stirring is effected for 30 minutes at room temperature. Then, 20 ml of acetone are added dropwise to the resulting crystal suspension over the course of 30 minutes. The suspension is cooled to 0°C. After stirring for 1 hour in an ice bath, the product is isolated and the filter cake is washed with acetone. After drying in a vacuum at room temperature, 0.742 g of the title compound are obtained in the form of a white crystalline powder.

HPLC purity: 99.5 area %

Example 4

Preparation of 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl)methoxyimino)acetyl]amino]-2-carboxy-8-oxo-5-

thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-pyrrolidinium dihydrochloride hydrate (cefepime dihydrochloride monohydrate)

1.706 g of pyrrolidinium-1-[(7-amino-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-yl)methyl]-dihydro-chloride are added to a mixture of 10 ml of $H_2O$ and 5 ml of methylene chloride, and the pH is adjusted to 6.50 by adding ion exchanger LA-2. The 2-phase mixture is cooled in an ice bath to 1°C. At this temperature, a solution of 4-chloro-2-methoxyimino-3-oxo-butyryl chloride, produced from 1.464 g of 4-chloro-2-methoxyimino-3-oxo-butyric acid (see example 1a), which has been cooled to -20°C, is added dropwise over the course of 1 hour, and the pH is maintained in the range of 6.0 to 6.5 by adding base LA-2. After stirring for 15 minutes in an ice bath, 0.76 g of thiourea are added and stirring is effected for 16 hours at 2-4°C. The pH is maintained in the range of 5.5 to 6.0 with LA-2. The reaction mixture is subsequently diluted with 100 ml of methylene chloride. After phase separation, the aqueous phase is washed with 50 ml of methylene chloride. The methylene chloride phases are combined and then extracted with 3 ml of $H_2O$. The product-containing aqueous phases are combined and mixed with 0.20 g of activated carbon. After stirring for 10 minutes, the activated carbon suspension is filtered. The carbon cake is washed with 1.5 ml of $H_2O$. The filtrate and washing water are combined and diluted with 60 ml of acetone. After adding seed crystals, stirring is effected for 30 minutes at room temperature. Then, 40 ml of acetone are added dropwise to the resulting crystal suspension over the course of 30 minutes. The suspension is cooled to 0°C. After stirring for 1 hour in an ice bath, the product is isolated and the filter cake is washed with acetone. After drying in a vacuum

at room temperature, 1.236 g of the title compound are obtained in the form of a white crystalline powder.

HPLC purity: 90.0 area %